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EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	PAPER NUMBER
1654	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,771	HOOK, VIVIAN Y.H.	
	Examiner	Art Unit	
	THOMAS S. HEARD	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/30/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-20* is/are pending in the application.

4a) Of the above claim(s) *2, 5-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Applicants Amendments to the claims received on 9/30/2008 is acknowledged. The text of those sections of Title 35 U.S. Code not included in the action can be found in the prior office action. Rejections or objections not addressed in this office action with respect to the previous office action mailed 3/31/2008 are hereby withdrawn.

Election/Restrictions

The response to Applicant's traverse of the Restriction requirement was overlooked in the previous office action. The Examiner apologizes for the mistake and corrects the mistake here. Applicant's election with traverse of Group I in the reply filed on 02/21/2007 and 10/30/2007 is acknowledged. The traversal is on the ground(s) that:

"[t]he Restriction Requirement is traversed with respect to the division of the claims of Group I from the claims of Group II. While the claims of Groups I and II are patentably distinct, it is submitted that a thorough search of the claims of either group will likely reveal art relevant to the examination of the claims of the other group. This is further indicated by the classification of the claims of Groups I and II in the same class (class 514). In particular, Groups II and II have been classified in the same class and subclass (class 514, subclass 2+). Thus, a search of the claims of Group I will, of necessity, reveal information relevant to the examination of the claims of Group II and, therefore, division of the claims into these groups would result in duplicative searches. Therefore, examination of the claims of Group I with the claims of Group II together should not be an undue burden on the Examiner."

This is not found persuasive because the inventions above are patentably distinct. For this reason alone restriction is proper. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. Thus, just because an invention can be classified together, burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for

foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement, and double patenting issues. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine all of the above inventions in one application and the restriction for examination purposes as indicated above is deemed proper.

The requirement is still deemed proper and is therefore made FINAL.

Claim(s) 2-20 are pending. Applicants have amended claim(s) 3 and added Claim 20. Claims 2 and 5-19 are withdrawn as being drawn to nonelected subject matter. Claims 3, 4, and 20 are hereby examined on the merits. Note that Claim 20 is being examined on only to the extent is reads on the elected species of Cathepsin B

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. V. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976);In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

Claims 3, 4, and the new Claim 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagao et al, "Synthesis of a new class of cathepsin B inhibitors exploiting a unique reaction cascade," Tetrahedron Letters, 41 (2000), 2419-2424 and Mackay EA et al "A possible role for cathepsins D, E, and B in the processing of beta-amyloid precursor protein in Alzheimer's disease," Eur J Biochem. 1997 Mar 1;244(2):414-25.

The instant claims are drawn to a method of selecting an agent that prevents the cleavage of an APP by the proteolytic action of cathepsin B.

Nagao et al teaches an assay where cathepsin B inhibitors are incubated in the presence of a cathepsin B peptide substrate, Z-L-Phe-L-Arg-MCA, see page 2421 and last paragraph for the assay. Nagao et al does not teach the use of APP as a cathepsin B substrate.

Mackay et al discloses the proteolytic action of cathepsin D, E, and B (Applicant's elected species), on the amyloid precursor protein (APP). Mackay et al teaches the use of MALDI-TOF mass spectroscopy to identify the position of cleavage of cathepsin D, E,

and B, see Figure 3 and Figure 5. Mackay et al does not teach the use of an inhibitor of cathepsin D, E, or B in the assay to inhibit the action of cathepsin B.

The difference between what is taught by the prior art and that instantly claimed is that the instant invention claims an assay to screen for inhibitors of cathepsin B toward APP, and the prior art teaches that there are cathepsin B inhibitor assays already developed but do not use APP as the substrate (Nagao et al) but that APP is a substrate of cathepsin B (Mackay et al).

It would have been obvious to one of ordinary skill in the art to modify the assay taught by Nagao et al to substitute the B peptide substrate, Z-L-Phe-L-Arg-MCA, with that of APP. One would have been motivated to do this because Mackay teaches that APP is a substrate for cathepsin B. One would have had a reasonable expectation of success in substituting APP for Z-L-Phe-L-Arg-MCA because cathepsin B can hydrolyze both Z-L-Phe-L-Arg-MCA and APP, and those inhibitors blocked cathepsin B and would also block the hydrolysis of APP. One would be further motivated to continue screening for compounds that inhibit the catalysis of APP because the hydrolytic fragments are known to be involved in the formation of Alzheimer's disease, and that one would be motivated to identify theses inhibitors for potential therapeutic use. Conversely, from the combined teaching of the Mackay et al and Nagao et al references, it would have been obvious to modify the Mackay et al teachings to add the inhibitors of Nagao et al, as well as any other compound, to determine whether the compound blocked cathepsin B activity and produced full length APP proteins as determined by MALDI-TOF mass spectroscopy. One would have a reasonable expectation of success because of the

detailed information revealed from MALDI-TOF mass spectroscopy, which include the position of cleavage by mass if the compound did not inhibit cathepsin B. From the teachings of the references supra, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, and the invention as claimed, is rejected under 35 U.S.C. 103(a).

Applicants arguments have been carefully considered but are not deemed persuasive to overcome the rejection. Applicants have argued the there is no motivation to combine the references. It is argued that there

"is no motivation to combine the two cited prior art references, which clearly show that the substrate used in the assays described by Nagao et al., which is a dipeptide capped at both ends, is distinct from the cleavage sites recognized by cathepsin B in the APP protein. Figure 6, panel C, shows the cleavage sites recognized by cathepsin B and not one of them consists of the amino acids F - Phenylalanine (Phe) and R - Arginine (Arg). Accordingly, the inhibition of enzymatic hydrolysis of a capped dipeptide that bears no resemblance to the cleavage sites recognized in the APP protein, would be considered unrelated and irrelevant by the skilled person, who would lack any motivation to combine their respective teachings.

This is not persuasive because the Mackay reference teaches that APP is a substrate for Cathepsin B. Just because the cleavage site is different between the two substrates, does not teach away from substituting APP for Z-L-Phe-L-Arg-MCA as both are substrates for the Cathepsin B. Therefore, one would have clear motivation to substitute one substrate for another in the assay. Applicant's amendments to the claim reciting a substrate comprising APP, is not sufficient to overcome the rejection because

a substrate comprising APP is still APP and the enzyme would still be a substrate for Cathepsin B. Therefore, the rejection is maintained for the reasons of record.

Conclusion

No claims are allowed.

Nucleotide Sequence and/or Amino Acid Sequence Disclosures

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below. **All sequences disclosed in the application must comply with the requirements of 37 C.F.R. 1.821-1.825, not only those recited in the claims.**

In the drawings submitted 3/22/2004, there are amino acids sequences that do not have proper identifiers. Applicants must have a SEQ ID associated with any amino acid sequence of four or more amino acids in length. Applicants should carefully check the specification to assure SEQ ID NOs are associated with all peptide four or more amino acids in length, even though they may not be claimed sequences.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Prior art contained in the reference of record can be applied in the next office action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be

applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas S. Heard** whose telephone number is **(571) 272-2064**. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thomas S Heard/
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654